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FOLEY, SHANON A	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 09/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/506,942	BALLOUL ET AL.	
	Examiner	Art Unit	
	Shanon Foley	1648	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 09 August 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 5 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☒ Applicant's reply has overcome the following rejection(s): 112, second paragraph.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see the attached correspondence*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *none*.

   Claim(s) objected to: *none*.

   Claim(s) rejected: *32,36,38,40,44,46,48,49,53-56,62,64,65,69,71-75,79 and 80*.

   Claim(s) withdrawn from consideration: *none*.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☒ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). *April 8, 2004*.

10. ☐ Other: _____

DETAILED ACTION

Response to Request for Reconsideration

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 32, 36, 38, 53 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lowy et al. (US 5,618,536), Hagensee et al. (Journal of Virology. 1993; 67 (1): 315-322), Borysiewicz et al. (Lancet. June, 1996; 347: 1523-1527), Galloway (Infectious Agents and Disease. 1994; 3: 187-193), and Meyer et al. (Journal of General Virology. 1991; 72: 1031-1038), as further evidenced by Boursnell et al. (US 5,719,054) for reasons of record.

With regard to the teachings of Lowy et al., applicant discusses the structure of the VLP of Lowy et al. and states that VLPs mimic infectious virions in structure and morphology and elicit neutralizing antibodies. However, applicant argues that Lowy et al. do not demonstrate any therapeutic protection against HPV-induced tumors with the VLPs comprising L1, L2 and E7.

In response, Lowy et al. are cited to provide explicit teachings that HPV polypeptides L1 and L2 induce protective efficacy, see column 2, lines 47-59 and example 9 in column 14. In addition, Lowy et al. specifically suggest incorporating E6 and E7 polypeptides into compositions to provide a therapeutic effect, see column 2, line 60 to column 3, line 16 and column 7, line 35-61. Express teachings of therapeutic

efficacy by E6 and E7 are found in the abstract and pages 190-191 of Galloway, page 1524 of Borysiewicz et al. and column 8, line 24 to column 10, line 12 of Boursnell et al. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Lowy et al. provide an express suggestion (i.e. motivation) to incorporate E6 and E7 into immunogenic compositions to provide a therapeutic effect and the teachings of Galloway, Borysiewicz et al. and Boursnell et al. expressly teach that HPV E6 and E7 induce a therapeutic effect with a reasonable expectation of success. Therefore, combining therapeutic HPV polypeptides E6 and E7 with the prophylactic HPV polypeptides L1 and L2 would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

With respect to the teachings of Borysiewicz et al. and Boursnell et al., applicant admits that Borysiewicz et al. and Boursnell et al. both disclose the use of HPV E6 and E7 genes for therapeutic purposes. Although applicant does not present arguments refuting the teachings of Borysiewicz et al., applicant argues that the overall teaching of Boursnell et al. promotes the fused expression of HPV polypeptide genes because only one of the options presented in the document (Figure 26c) depicts unfused expression. Applicant also points to the paragraph bridging columns 9 and 10 of Boursnell et al. stating that expression of four gene sequences could be difficult to achieve as independent expression units.

Applicant's arguments have been fully considered, but are found unpersuasive. In the same sentence applicant refers to, Boursnell et al. also clearly state that the expression

of the four gene sequences would not be impossible, see column 9, lines 65-66 and provides four examples of four HPV nonfused genes in Figure 26c (also see column 3, lines 29-35 and column 8, lines 24-37). In addition, the explanation provided by Boursnell et al. for why expression may be difficult is provided in the sentences following the sentence cited by applicant. Boursnell et al. explain that the inclusion of genes for selectable markers had previously interfered with foreign gene insertion in the vaccinia virus genome, but that methods of insertion have been developed to allow elimination of the extraneous marker sequences, see column 10, lines 1-8. The instant claims do not allow for any extraneous marker sequences since the claims are drawn to a composition consisting of an MVA vector (taught by Meyer et al.) coding for E6, E7, L1 and L2 genes under individual expression control elements.

Applicant argues that Galloway reviews clinical studies involving late papillomavirus polypeptides as fusion proteins and individual papillomavirus polypeptides. Applicant emphasizes that the instant invention is drawn to expressing E6, E7, L1 and L2, each from independent expression control elements in an MVA vector.

Applicant's arguments have been fully considered, but are found unpersuasive. Although Galloway mentions "L1 or L2 fusion proteins" in the alternative in the second column on page 190, the reference does not specify what L1 or L2 are fused to. Since Galloway mentions the proteins in the alternative, they are obviously not fused to each other. Galloway also reviews vaccinia virus recombinants alternatively expressing early genes that retard the development of tumors, see the paragraph bridging pages 190-191.

The teachings of Galloway, refuted by applicant to be deficient for teaching all of the limitations in the instant claims, is not cited to provide teachings of fused versus

unfused papillomavirus polypeptides in an MVA vector. These limitations are taught in other references. The teachings of Galloway are provided to demonstrate that the early proteins, E6 and E7 are therapeutic and that the late proteins, L1 and L2, are prophylactic. This teaching, in combination with the other references cited in the instant rejection, provide all of the limitations in the claims, as well as a motivation for the combination with a reasonable expectation of success for producing the invention once combined. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant reiterates the subject matter of the claims and argues that the elements of the instant invention are not disclosed or suggested by the cited references.

Applicant's arguments have been considered, but are found unpersuasive. The elements of the instant invention are as follows:

A composition consisting of:

A recombinant modified Ankara vector (MVA)

- Meyer et al. teach the vaccinia virus strain MVA, see pages abstract and pages 1032-1034.

with DNA sequences coding for (i) the early E6 and (ii) early E7 polypeptides of a papillomavirus and

- Galloway reviews the state of the art at the time the invention was made and teaches that the early papillomavirus polypeptides E6 and E7 are therapeutic in nature, see the abstract and pages 190-191.

- Lowy et al. suggest incorporating early papillomavirus polypeptides E6 and E7 into compositions to provide a therapeutic effect, see column 2, line 60 to column 3, line 16 and column 7, lines 35-61.
- Boursnell et al. claim a recombinant vaccinia virus vector expressing E6 and E7 early papillomavirus genes, see claims 1-3, 5, 8 and 12.
- Borysiewicz et al. teaches expression of early papillomavirus polypeptides E6 and E7 from a vaccinia virus vector to treat cervical cancer, see page 1524.

(iii) the late L1 and (iv) the late L2 polypeptide of the papillomavirus

- Galloway reviews the state of the art at the time the invention was made and teaches that the late papillomavirus polypeptides L1 and L2 are prophylactic in nature, see the abstract and pages 190-191.
- Lowy et al. teach a DNA molecule directing the expression of papillomavirus late polypeptides, L1 and L2, see claims 16, 17 and column 4, line 62 to column 5, line 2 to lines 6-9. Lowy et al. also teach that the papillomavirus late polypeptides are prophylactic, see column 2, lines 60 to column 3, line 16, column 7, lines 35-61 and example 9 in column 14.
- Hagensee et al. teach expressing papillomavirus late L1 and L2 proteins in a vaccinia virus, see pages 316-317.

wherein each of the DNA sequences under the control of independent expression elements

- Boursnell et al. clearly demonstrate the expression of four different papillomavirus gene sequences from different promoters in a vaccinia virus vector, see Figure 26c, column 3, lines 29-35 and column 8, lines 24-37.

the promoter necessary for the expression of the DNA sequences are: 7.5K and K1L genes

- Hagensee et al. teach expressing the late papillomavirus polypeptides, L1 and L2, in a vaccinia virus vector from a 7.5K promoter, see pages 316-317.
- Borysiewicz et al. teach expressing early papillomavirus polypeptides, E6 and E7, from a 7.5K promoter in a vaccinia virus vector, see page 1524.
- Meyer et al. teach that the insertion of the K1L genes in the MVA vaccinia strain leads to increased host range, see page 1037.

the DNA sequences are inserted into at least one excision region of MVA selected from: I, II, III, IV, V, VI and VII

- Meyer et al. teach six major deletion sites, I, II, III, IV, V and VI, that are not essential to virus replication in the wild-type Ankara strain and attenuates virus pathogenicity to MVA, see page 1032-1034.

a method of treating or preventing papillomavirus infection, dysplasia or cancer of the neck of the uterus by administering an effective amount of the composition and a pharmaceutically acceptable carrier

- Galloway reviews the state of the art at the time the invention was made and teaches that the late papillomavirus polypeptides L1 and L2 are prophylactic in nature, see the abstract and pages 190-191.
- Lowy et al. teach protection against papillomavirus infection with late polypeptides, L1 and L2, see column 2, line 47 to column 3, line 16, column 7, lines 35-61 and example 9 in column 14.

- Galloway reviews the state of the art at the time the invention was made and teaches that the early papillomavirus polypeptides E6 and E7 are therapeutic in nature, see the abstract and pages 190-191.
- Borysiewicz et al. teach expression of early papillomavirus polypeptides E6 and E7 from a vaccinia virus vector to treat cervical cancer, see page 1524.

Therefore, contrary to applicant's assertion, the combination of prior art references cited do teach every element of the claimed invention. Applicant has not pointed to an element in the instant claims that is not expressly taught by the combination of references.

Applicant asserts that there is no way of knowing whether independent expression of both early and late polypeptide genes from an MVA vector would enable appropriate presentation of the papillomavirus antigens to the host's immune system to confer antitumor activity.

Applicant's assertion has been considered, but is found unpersuasive since the data presented combination of references indicates an antitumor activity. As discussed above, Galloway reviews the state of the art and concludes that papillomavirus polypeptides E6 and E7 are therapeutic and L1 and L2 have protective properties. Borysiewicz et al. teach expression of early papillomavirus polypeptides E6 and E7 from a vaccinia virus vector to treat pre-existing cervical cancer, see page 1524 and Hagensee et al. teach expressing papillomavirus late L1 and L2 proteins in a vaccinia virus, see pages 316-317. Although Hagensee et al. do not teach protective efficacy with L1 and L2, Lowy et al. do, see column 2, line 47 to column 3, line 16, column 7, lines 35-61 and example 9 in column 14. Although Borysiewicz et al., Hagensee et al. and Lowy et al. do

not teach expressing each of the four papillomavirus polypeptides, E6, E7, L1 and L2 from individual expression control elements from a vaccinia vector, Boursnell et al. clearly demonstrate the expression of four different papillomavirus gene sequences from different promoters in a vaccinia virus vector, see Figure 26c, column 3, lines 29-35 and column 8, lines 24-37. The vaccinia virus vector of Boursnell et al. is not MVA. However, Meyer et al. teach six major deletion sites, I, II, III, IV, V and VI, that are not essential to virus replication in the wild-type Ankara strain and attenuates virus pathogenicity to MVA, see page 1032-1034.

The combination of references clearly shows that expression of papillomavirus early polypeptides, E6 and E7, expressed from a vaccinia virus vector results in a therapeutic effect and that expression of papillomavirus late polypeptides, L1 and L2, expressed from a vaccinia vector, results in a prophylactic effect. Independent expression of four different papillomavirus polypeptides in a vaccinia virus vector is also expressly taught.

Therefore, it is maintained that one of ordinary skill in the art at the time the invention was made would have been motivated to express the HPV polypeptides of Lowy et al., Hagensee et al., Borysiewicz et al. and Galloway in the MVA vector of Meyer et al. under the control of different promoters, taught by Boursnell et al. to express the proteins from independent control elements in order to control transcription and subsequently, the amount of protein expressed in the cell. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of producing the construct claimed because Boursnell et al. teach individual expression of different HPV polypeptides in a vaccinia vector and MVA of Meyer et al. is a vaccinia vector.

Applicant states that the neutralizing antibodies of Lowy et al. are not predictive for using an MVA vector to treat pre-existing tumors.

In response, Lowy et al. do not teach an MVA vector, Meyer et al. do. Further, Lowy et al. teach protective efficacy of papillomavirus polypeptides, L1 and L2, not treatment of pre-existing tumors. Galloway teaches that the early papillomavirus polypeptides E6 and E7 are therapeutic, see the abstract and pages 190-191 and Borysiewicz et al. teaches expression of early papillomavirus polypeptides E6 and E7 from a vaccinia virus vector to treat cervical cancer, see page 1524.

Applicant emphasizes that E6 and E7 are nuclear polypeptides and that the instant MVA vector enables production of papillomavirus antigens inside the host cells and are accessible to the immune system. Applicant contrasts this concept with the teachings of Lowy et al., teaching the presentation of E7 on the surface of a VLP surface. Applicant argues that using chimeric VLPs for delivering E7 into an HPV-infected patient is likely to reduce the E7-mediated immune response due to the neutralization of pre-existing anti-L1 antibodies present in HPV-infected patients. Applicant also discusses the antibody response against E7 in Galloway and further concludes that the development of a humoral immune response may not correlate with a protective effect. Applicant concludes that references teaching the fusion of early polypeptides to a late polypeptide (L2), would not motivate the skilled artisan to make unfused early and late polypeptides.

Applicant's arguments and a review of the references have been fully considered, but are found unpersuasive. Fusing E7 to the surface of a VLP is not instantly claimed. It is clear that no fusion is claimed, i.e. E7 to L2. The teachings of Lowy et al. are provided to demonstrate that the late polypeptides, L1 and L2, induce a protective effect.

Galloway arrives at the same conclusion in the review article presented. The teachings of Lowy et al. are also not cited for teaching therapeutic efficacy because the reference does not include those essential polypeptides, E6 and E7, into the composition. The inclusion of E6 and E7 in the composition of Lowy et al. to provide therapeutic efficacy is only suggested. Both Lowy et al. and Galloway separately teach protection against papillomavirus infection with L1 and L2, not treating a previously infected host with the two proteins. Neither Lowy et al. nor Galloway are cited for teaching expression of these prophylactic proteins in a vaccinia virus vector, i.e. MVA, because Hagensee et al. teach the expression of L1 and L2 from a vaccinia vector and Meyer et al. teach an MVA vector.

Applicant further concludes that the cited references do not teach the claimed invention.

However, this argument has been rendered moot, see above.

Applicant also argues that there is no motivation provided in the references to use an MVA vector to express early and late non-fused papillomavirus polypeptides. Applicant bases this conclusion from the references teaching insertion of early HPV polypeptides into L2 in order to improve accessibility to the host's immune system and that the expression of multiple genes from independent promoters in a single vaccinia virus vector could be difficult to achieve.

In response to the first argument, it is obvious that the insertion of early HPV into L2 to improve accessibility to the immune system is unfounded since the single combination of L1 and L2 induce a protective immune response, see the teachings of Lowy et al. and Galloway. In addition, expression of L1 and L2 from a vaccinia virus

vector, taught by Hagensee et al., results in the presentation of the required conformational epitopes for protective efficacy.

In response to the second argument, Boursnell et al. provide four examples of four HPV nonfused genes in Figure 26c (also see column 3, lines 29-35 and column 8, lines 24-37). Boursnell et al. also explain that expression may be difficult in vaccinia vectors if selectable marker genes are included within the construct. However, Boursnell et al. also teach that methods of insertion have been developed to allow elimination of the extraneous marker sequences, see column 10, lines 1-8. Further, the instant claims do not allow for any extraneous marker sequences since the claims are drawn to a composition consisting of an MVA vector (taught by Meyer et al.) coding for E6, E7, L1 and L2 genes under individual expression control elements. Therefore, the remote concern that multiple gene expression may be problematic in vaccinia vectors is eliminated by the new methods of insertion, discussed by Boursnell et al., and the fact that the instant vector does not include any extraneous selectable marker sequences.

Although applicant mentions the teachings of Meyer et al. and Hagensee et al., applicant does not argue the limitations expressly taught by the references, the motivation for combining the teachings of Meyer et al. and Hagensee et al. with Lowy et al., Borysiewicz et al., Galloway and Boursnell et al., or the reasonable expectation the ordinary artisan would have upon such a combination.

Claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lowy et al. (US 5,618,536), Hagensee et al. (Journal of Virology. 1993; 67 (1): 315-322), Borysiewicz et al. (Lancet. June, 1996; 347: 1523-1527), Galloway (Infectious Agents and Disease. 1994; 3: 187-193), and Meyer et al. (Journal of General Virology. 1991; 72:

1031-1038), as further evidenced by Boursnell et al. (US 5,719,054), as applied to claims 32, 36, 38, 53 and 54 above, and further in view of Crook et al. (Cell. 1991; 67: 547-556) and Munger et al. (EMBO Journal. 1989; 8: 4099-4105) for reasons of record.

The inclusion of claims 57 and 58 in the previous rejection was an inadvertent typo, as evidenced by the Office action summary.

Applicant resubmits that in reference to the arguments presented for claim 32, none of the references provide disclosure or motivation for the skilled artisan to use an MVA vector independently expressing nonfused E6, E7, L1 and L2.

Applicant's arguments have been fully considered, but are found unpersuasive. One of skill in the art at the time of the invention would have been motivated to combine E6 and E7 of Borysiewicz et al. into the vaccinia vector of Hagensee et al. expressing the L1 and L2 proteins of Lowy et al. to treat and prevent papillomavirus infection in a host with the same administrative composition (emphasis added). One of skill in the art at the time of the invention would also have had a reasonable expectation of success for producing the claimed invention because L1 and L2 possess prophylactic properties (discussed by Lowy et al. and Galloway) and E6 and E7 possess ameliorative properties (discussed by Borysiewicz et al. and Galloway) (emphasis added).

One of ordinary skill in the art at the time the invention was made would have been motivated to express the HPV polypeptides of Lowy et al., Hagensee et al., Borysiewicz et al. and Galloway in to the MVA vaccinia vector of Meyer et al. under the control of different promoters, taught by Boursnell et al. to express the proteins from independent control elements in order to control transcription and subsequently, the amount of protein expressed in the cell. One of ordinary skill in the art at the time the

invention was made would have had a reasonable expectation of producing the construct claimed because Boursnell et al. teach individual expression of different HPV polypeptides in a vaccinia vector and MVA of Meyer et al. is a vaccinia vector.

Claims 44, 46, 48, 55, 56, 62 and 64 rejected under 35 U.S.C. 103(a) as being unpatentable over Lowy et al. (US 5,618,536), Hagensee et al. (Journal of Virology. 1993; 67 (1): 315-322), Borysiewicz et al. (Lancet. June, 1996; 347: 1523-1527), Galloway (Infectious Agents and Disease. 1994; 3: 187-193), and Meyer et al. (Journal of General Virology. 1991; 72: 1031-1038), as further evidenced by Boursnell et al. (US 5,719,054), as applied to claims 32, 36, 38, 53 and 54 above, and further in view of Bubenik et al. (International Journal of Oncology. 1996; 8: 477-481) for reasons of record.

Applicant states that animals vaccinated with irradiated cells and IL-2 were protected to a greater extent than animals treated with irradiated cells only.

Applicant is correct and this is precisely why this reference is cited. Bubenik et al. teach a limitation that is not taught by the other references in the rejection, i.e. the administration of IL-2. Bubenik et al. not only teach the limitation that is not taught by the other references in the instant rejection, Bubenik et al. also provide a motivation to incorporate IL-2 in a papillomavirus vaccine since the data of Bubenik et al. clearly demonstrate that IL-2 enhances immunization against papillomavirus infection, see the abstract, the materials and methods section on page 478, Figure 1 on page 479 and the discussion section. This phenomenon is also admitted by applicant.

Applicant argues that Bubenik et al. administer two injections of irradiated cells and separately, 20 injections of IL-2 to animals before being challenged with tumor cells.

Applicant asserts that this method would be difficult to implement in human patients. Applicant submits that the Office is incorrect that multiple injections of IL-2 provides another motivation for the ordinary artisan to express the cytokine in the MVA expression construct because Bubenik et al. require huge quantities of IL-2. Applicant states that the assertion by the Office that the expression of IL-2 would enable the quantity required for inducing an adjuvanting effect is speculative. Applicant argues that there is no way of knowing how to produce the huge quantities of IL-2 required to influence the effect of the papillomavirus vaccine. Applicant concludes that a reasonable expectation of success for administering an MVA vector expressing E6, E7, L1 and L2 is not found in the teachings of Bubenik et al.

Applicant's arguments and a review of the reference has been fully considered, but is found unpersuasive. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found ***either*** 1) in the references themselves or 2) in the knowledge generally available to one of ordinary skill in the art (emphasis added). See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, motivation for expressing IL-2 in the instant MVA vector claimed is taught by Bubenik et al. The reference explicitly teaches and provides indisputable data that IL-2 enhances immunization against papillomavirus infection. The ordinary artisan would be motivated to augment the immune response with IL-2 against papillomavirus polypeptides expressed by a papillomavirus vaccine vector. As noted

above, only one motivation is required. However, in the instant case, there is yet another reason for expressing IL-2 in the MVA vector of Meyer et al., Lowy et al., Hagensee et al., Borysiewicz et al., Galloway and Boursnell et al. As applicant points out, Bubenik et al. administers 20 separate injections of IL-2 in the protocol disclosed. Administering as many separate injections is not practical for human administration. Therefore, the ordinary artisan would be motivated to incorporate IL-2 in the instant expression vector to avoid requiring repeated journeys of patients to a facility for multiple administrations. This motivation would be found in the knowledge generally available to one of ordinary skill in the art.

Regarding the lack of a reasonable expectation of success for expressing the huge quantities of IL-2 administered by Bubenik et al. applicant refers to, expression of IL-2 from the vector of Meyer et al., Lowy et al., Hagensee et al., Borysiewicz et al., Galloway and Boursnell et al. would be continuous. The amount of IL-2 administered to laboratory mice to achieve the adjuvanting effect observed by Bubenik et al. would be different from the amount required to achieve the same effect in humans. The amount required to achieve this effect is not a recited element of the claims. In addition, it is noted that differences in concentrations will not support the patentability of subject matter unless there is some evidence indicating that the required concentration is critical to the invention. See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

The instant claims require expressing papillomavirus polypeptides and a DNA sequence encoding a polypeptide having immunostimulatory activity, wherein the polypeptide is IL-2, see instant claims 44 and 46. Bubenik et al. clearly establishes that IL-2 has immunostimulatory activity and possesses adjuvanting properties against

papillomavirus infection. The amount of vector required to be administered to achieve the optimum adjuvanting effect of IL-2 would be a matter of routine experimentation. Applicant's argument that the Office is only speculating that the expression of IL-2 would enable the quantity required for inducing an adjuvanting effect leads the examiner to wonder if applicant is questioning the predictability and quantity of experimentation that would be required to practice the instant invention since applicant also asserts that there is no way to know how to produce the quantities of IL-2 required to influence the immune response in the instant vector composition. It would appear from the teachings in the prior art that this is not the case because the papillomavirus polypeptides required to treat, i.e. E6 and E7, and prevent, i.e. L1 and L2, infection are known. It is also established in the prior art of record that the vaccinia virus vector is an efficient carrier of multiple papillomavirus polypeptide genes and is able to express them simultaneously and in any orientation (i.e. not fused) to induce an effective immune response. It is also established in the prior art that IL-2 induces an effective adjuvant response in a host with compositions against papillomavirus. The ability to express IL-2 from a vaccinia vector is undisputed. The amount of IL-2 required to be expressed from the vector is not claimed and would be a matter of routine optimization in the art. Therefore, a reasonable expectation of success for one of ordinary skill in the art for combining all of the elements, known in the art to be effective against papillomavirus infection, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

Claim 49 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lowy et al. (US 5,618,536), Hagensee et al. (Journal of Virology. 1993; 67 (1): 315-322),

Borysiewicz et al. (Lancet. June, 1996; 347: 1523-1527), Galloway (Infectious Agents and Disease. 1994; 3: 187-193), Meyer et al. (Journal of General Virology. 1991; 72: 1031-1038), as further evidenced by Boursnell et al. (US 5,719,054), and Bubenik et al. (International Journal of Oncology. 1996; 8: 477-481) as applied to claims 32, 36, 38, 44, 46, 48, 53-56, 62 and 64 above, and further in view of Crook et al. (Cell. 1991; 67: 547-556) and Munger et al. (EMBO Journal. 1989; 8: 4099-4105) for reasons of record.

Applicant reiterates the arguments presented for claim 48, from which claim 49 depends.

These arguments are found unpersuasive and the rejection is maintained for reasons of record. The rebuttal for these arguments is repeated herein.

Claims 65, 69, 71, 72, 74, 79 and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Borysiewicz et al. (Lancet. June, 1996; 347: 1523-1527), Meyer et al. (Journal of General Virology. 1991; 72: 1031-1038) and Bubenik et al. (International Journal of Oncology. 1996; 8: 477-481), as further evidenced by Boursnell et al. (US 5,719,054).

Applicant reiterates the summary of the invention. Applicant argues that Boursnell et al. teaches that expressing multiple genes from independent promoters can be difficult to achieve. Applicant also argues that Bubenik et al. fails to provide a reasonable expectation of success since there would be no way of knowing how to produce huge quantities of IL-2 necessary to influence the immune response since Boursnell et al. teach that expressing more than 2 expression units can be difficult to achieve.

Applicant's arguments have been fully considered, but are found unpersuasive. As pointed out in further teachings of Boursnell et al., difficulties expressing multiple genes from independent promoters is not a hindrance due to new methods briefly mentioned in the reference that eliminate the need for marker genes. Boursnell et al. also expressly illustrate the expression of four different papillomavirus genes from a vaccinia virus vector in Figure 26c.

Regarding the quantity of IL-2 administered to mice by Bubenik et al. to induce an augmenting immune response, Bubenik et al. explicitly teach that IL-2 induces an adjuvanting effect when administered with a composition against papillomavirus. The amount of IL-2 required to be expressed from the instant vector is not a required element. Further, the amount of expression from the instant vector and the amount of vector administered would be of routine design by one of ordinary skill.

Claim 75 is rejected under 35 U.S.C. 103(a) as being unpatentable over Borysiewicz et al. (Lancet. June, 1996; 347: 1523-1527), Meyer et al. (Journal of General Virology. 1991; 72: 1031-1038) and Bubenik et al. (International Journal of Oncology. 1996; 8: 477-481) as applied to claims 65, 69, 71, 72, 74, 79 and 80 above, and further in view of Crook et al. (Cell. 1991; 67: 547-556) and Munger et al. (EMBO Journal. 1989; 8: 4099-4105), as further evidenced by Boursnell et al. (US 5,719,054) for reasons of record.

The inclusion of cancelled claims 76 and 77 in the previous rejection was an inadvertent typo, as evidenced by the Office Action Summary sheet.

Applicant reiterates that none of the cited references teach or motivate the skilled artisan to use an MVA vector expressing nonfused papillomavirus polypeptides and an immunostimulatory polypeptide.

These arguments were considered above, but were found unpersuasive. The rebuttal for these arguments is resubmitted herein.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (571) 272-0898. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Shanon Foley
Patent Examiner, 1648